STRUCTURAL AND FUNCTIONAL ORGANIZATION OF MAMMALIAN CEREBRAL CORTEX: THE CORRELATION OF NEURONE DENSITY WITH BRAIN SIZE

CORTICAL NEURONE DENSITY IN THE FIN WHALE (BALAENOPTERA PHYSALUS L.) WITH A NOTE ON THE CORTICAL NEURONE DENSITY IN THE INDIAN ELEPHANT

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SIX FIGURES

INTRODUCTION

Both Nissl (1898) and von Bonin ('48) have remarked that an increase in brain size seemed to be associated with a decrease in the density of neurones in the cerebral cortex. Until recently quantitative data on cortical neurone density have been lacking.

In their study of the activity of the acetylcholine system in the cerebral cortex of various mammals, Tower and Elliott ('52a) found that values for all components of the acetylcholine system decreased regularly with increasing brain size. The decrease was correlated with the average total brain weight of each species and was the same function of brain weight for all types of activity measured. The equation characterizing this relationship was $A = K_A W^k$ (where A is the particular activity per unit weight; K_A is a constant characteristic of the particular activity measured; W is average total brain weight; and k is the regression coefficient for the logarithm of A versus the logarithm W for the various species).

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In all cases the value for k was found to be approximately -0.3.

The possibility that decrease in activity of the acetylcholine system might be related to decrease in neurone density was tested. It was found that a decrease in the number of neurones per unit volume of cortex with increasing brain weight gave a similar regression curve (Tower and Elliott, '52a). The number of nerve cells per unit volume, N, was given by $N = K_N W^k$ with k being approximately -0.3. These data were obtained on a variety of mammals from mouse to man.

Subsequently Shariff ('53) has reported data on cell counts in cerebral cortices of primates, ranging from *Tarsius* to man, determined by a different method. Calculations based on his figures gave a value for the regression coefficient, k, of approximately -0.3 (Tower and Elliott, '52a).

In their paper Tower and Elliott pointed out that no species with a brain weight greater than man had been studied. To test the validity of these observations investigation of elephant or cetacean cerebral cortex would be required. It has now been possible through the very kind cooperation of Dr. Jan Jansen of the Anatomical Institute, University of Oslo, to determine neurone densities in the cerebral cortex of the adult fin whale (*Balaenoptera physalus* L.). In addition a few observations on the cerebral cortex of the Indian elephant have been possible.

The brains of the large whales are some 5 times the size of human brain. Very little, particularly from an histological standpoint, is known regarding the central nervous system of the cetacea. In Guldberg's (1885) monograph on the gross anatomy of the central nervous system of the larger cetacea directions are given for the technique of brain removal together with observations that the body temperature of the whale may remain elevated for hours to days following death. Mettler ('52) has observed that in the elephant the internal temperature may actually rise after death. The difficulties in removal of the brains plus the long maintenance of elevated body temperature *post mortem* in these large mammals undoubtedly account for the paucity of microscopic studies of their brains.

To our knowledge only one report on the microscopic appearance of the cerbral cortex of the larger species of whales has appeared, viz. that of Kojima ('51).

MATERIALS AND METHODS

Two brains of adult fin whales (*Balaenoptera physalus* L.) were collected fresh by Dr. Jansen at Sæbjørnsen's whaling station, Steinshamn on the Norwegian west coast, during the summer of 1952. The first (Cst I) came from a 68-foot female fin whale and weighed 6500 gm (fresh) with pia-arachnoid. The second (Cst II) came from a 54-foot male fin whale and weighed 7100 gm (fresh) with pia-arachnoid. Both these brains were fixed immediately in formalin. A third brain (C293), which had been fixed in formalin for over a year, had come from a 67-foot male fin whale collected in the Antarctic by Norwegian whaling ship control officers. It weighed 7150 gm (fixed) with pia-arachnoid (Jansen, '52). Paraffin sections, cut at 20 μ, were prepared from the first and third brains and stained for Nissl substance with Gruebler's cresyl-violet.[2] In both cases sections were taken from various regions of the cortex.

Three sections of cerebral cortex, cut at 20 μ, and stained for Nissl substance, from an Indian elephant were made available through the kindness of Dr. Gerhardt von Bonin. These sections were prepared from the brain (M 140-43) of the 50-year-old female elephant "Alice" of Luna Park, New York City. The brain was removed by Dr. Fred Mettler and weighed 6075 gm after brief fixation in formalin, without dura. This brain was removed under very favorable circumstances and is probably more represenative of the true size and anatomy of the elephant brain than those previously studied under adverse "field" conditions. The brain weight is higher than the average of 4400 gm reported by Count ('47).

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[2] A few sections of the third brain (C293) were cut at 15 μ and stained for Nissl substance with thionine for preliminary study. Since the results of neurone counts on these sections were similar to those obtained with 20 μ cresyl-violet stained sections, they have been included as well.

All microscopic sections were photographed at a magnification of × 60 with a Zeiss horizontal photomicrograph unit. With the aid of the photomicrographs, neurones were counted in segments of the original sections, using an ocular fitted with a standard field grid. All sections had been cut at right angles to the pial surface and the counts were made from pia to white matter. In each section a total of 800 to 1500 neurones were counted, only those with visible nucleoli being included. The number of neurones in 1 mm^2 of 20 μ section was calculated and multiplied by 50 to obtain the density per cubic millimeter, which represented the average cell density throughout the various cortical layers. This method is essentially that of Tower and Elliott ('52a) with slight modifications for the lesser densities encountered.

The absolute accuracy of these counts is not considered to be great. By use of sections cut at the same thickness, stained by the same technique and technician, and counted in the same manner by the same observer, as those previously reported (Tower and Elliott, '52a), relatively standard conditions could thus be assured. The results probably give a fairly true idea of the *relative* cell populations, with any error being kept within fairly constant limits.

RESULTS

Neurone density. Neurone densities were determined in a total of 14 sections of cerebral cortex prepared from various regions of the two fin whale brains (Cst I and C293). In the absence of any knowledge regarding cortical localization in the whale, it is impossible to state from which cortical area most of these sections were taken.[3] The sections were reasonably distributed among dorsal, lateral and medial surfaces of the hemispheres, both antero-posteriorly and dorso-ventrally. Only one section (plate 1) could be identified grossly as being taken from an area corresponding to the anterior cingulate gyrus. A second section (plate 3) was taken from a region,

[3] The sections were kindly examined by Dr. Jerzy Olszewski of the Neuroanatomy Laboratory, Montreal Neurological Institute. He was unable, on cytoarchitectonic grounds, to identify any areas analogous to typical areas in other mammalian species.

which grossly might be considered to correspond to some portion of the parietal cortex, posterior to the primary somatic sensory area. Beyond these, localizations were not attempted.

The neurone densities in all 14 sections ranged between 6500 and 7100 neurones per cubic millimeter, with an average for all sections of 6800 per cubic millimeter. In view of the narrow range of densities it has seemed justifiable to adopt the average value. In their paper Tower and Elliott ('52a) determined densities in sections of agranular cortex (motor cortex). In the present study, since motor cortex could not be identified in any section, no direct comparison with the previous data can be made. Whether the neurone density as determined for fin whale cortex may be compared with those of Tower and Elliott for motor cortex of other mammals is a fair question. The marked lack of variation in neurone density from a number of different cortical sites in fin whale cortex would seem to justify the use, with reservations, of the average value for such comparison.

A similar problem arises in connection with the sections of elephant cortex available for study. No localizations grossly or cytoarchitectonically could be determined for these sections. The neurone densities in the three sections ranged from 6700 to 7100 neurones per cubic millimeter, with an average of 6900 per cubic millimeter. This figure is included for comparison, with similar reservations.

Correlation with brain weight. Very few values for brain weights of fin whales are available. In addition to the three mentioned above (6500, 7100 and 7150 gm respectively), the weights (after formalin-fixation) of 4 other brains of adult fin whales were 5970, 6900, 6820 and 7875 gm respectively all with pia-arachnoid (Jansen, '52). Only two other reliable weights have been found in the literature. Guldberg (1885) reported a brain weight of 6700 gm (fresh) without dura for a 60-foot *Balaenoptera musculus* COMPANY (= *B. physalus* L.)[4] and

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[4] Confusion in species nomenclature is commonly met with in older Zoological references. The generally accepted classification of cetacean species at present is given by Norman and Fraser ('49), together with distinguishing characteristics of each species. From their data, it is usually possible to determine which species is indicated in well-documented reports.

Ries and Langworthy ('37) found a brain weight of 5950 gm (fixed) for an adult *Balaenoptera physalus.* The average of these 9 values is 6785 gm, the figure used in this study. (Values for brain weights of other large species of whales approximate this figure: *Balaenoptera musculus* SIBBALDI (the blue whale) — 6800 gm (Crile and Quiring, '40); *B. Sulfurea* (= *B. musculus* SIBB.) — 5678 gm (Wilson, '33); *Physeter catodon* (the sperm whale) — 7000 and 7980 gm (Ries and Langworthy, '37); 6400 to 9200 gm, with an average of 7800 gm for 16 brains (Kojima, '51).

With an average brain weight of 6785 gm for the fin whale, it can be predicted by extrapolation of the published curve of Tower and Elliott ('52a) that the neurone density of fin whale agranular cortex would be about 4800 per cubic millimeter. Calculation of the neurone density from their formula gives a value of 6450 per cubic millimeter. (The difference is due to the slight deviation of the published curve from that calculated from the formula derived from the average values.) The density obtained by direct counts of sections closely approximates the calculated value.

No satisfactory brain weight values for the elephant were available. On the basis of the single weight of 6075 gm for the specimen used here, an extrapolated value of 5000 neurones per cubic millimeter and a calculated value of 6750 neurones per cubic millimeter are obtained. The observed density closely approximates this latter figure.

The average neurone densities for fin whale and elephant cortices, together with the densities previously reported for other mammals by Tower and Elliott ('52a), have been plotted against the respective average total brain weights on double logarithmic scales. The resulting graph is shown in figure 1. Using the method of least squares, the theoretical slope has been calculated from the logarithms of the values. The value for k, the regression coefficient, calculates as -0.32, which is in excellent agreement with the value of $k = -0.35$ previously obtained (Tower and Elliott, '52a) and with the value of $k = -0.28$ calculated from the revised data of Shariff ('53). As

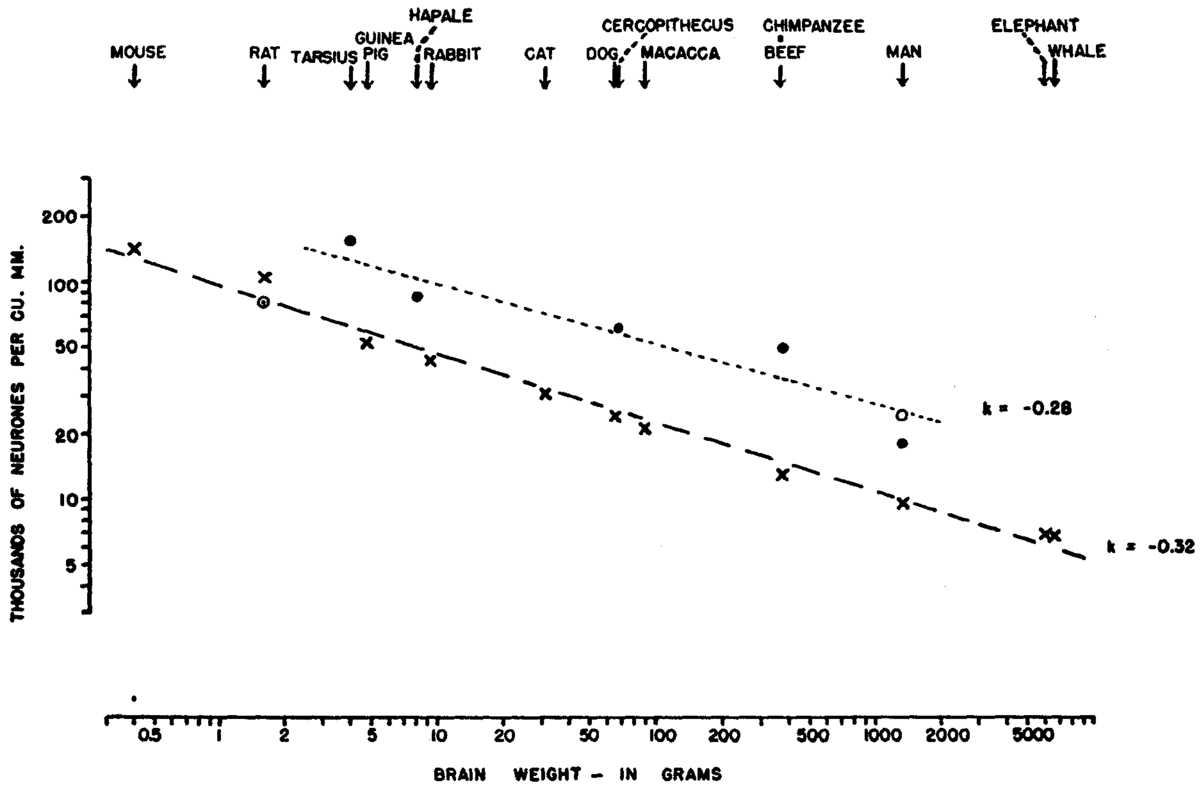

Fig. 1 Neurone density in the cerebral cortex of various adult mammals in relation to average total brain weight (Log Scales). × = Values from Tower and Elliott ('52a) and present study for species with the following average total brain weights (from Count, '47 with the exception of elephant and whale): Mouse 0.4 gm, rat 1.6 gm, guinea pig 4.75 gm, rabbit 9.3 gm, cat 31 gm, dog 65 gm, monkey *(Macacca)* 88.5 gm, beef 375 gm, man 1320 gm, elephant 6075 gm, and fin whale 6785 gm.
● = Values from Shariff ('53) for agranular cortex of primate species with the following average total brain weights (from Count, '47 and Shariff, '53): *Tarsius* 4 gm, *Hapale* 8 gm, *Cercopithecus* 67 gm, chimpanzee 375 gm, and man 1320 gm.
⊙ = Value averaged from data of Sugita ('18a) for rat cortex.
○ = Value calculated from data of von Economo ('26) for human cortex.
The regression coefficients, k, for the equation, $N = K_N W^k$ are shown beside each regression line.

before the correlations between the logarithms of neurone density and of brain weight, as given in figure 1, were highly significant ($r = -0.994$; for $N = 8$, $P < 0.001$). [The neurone densities for human cortex were not included in the calculations, since the material was deliberately taken from patients with focal cortical seizures for another purpose (Tower and Elliott, '52b). The plotted average for man, however, falls very close to the calculated theoretical slope].

For visual comparisons the accompanying photographs have been included. Figure 2 shows the relative sizes of the formalin-fixed gross brains of normal adult man and of the fin whale (C293) at the same magnification. Good photographs of various aspects of the gross brains of *Balaenoptera physalus* L. have been published by Ries and Langworthy ('37) and Langworthy ('35). Microscopic sections (× 60) from normal adult human cerebral cortex and from fin whale cortex (Cst I) are illustrated in plates 1–4. All sections were prepared and photographed under the same conditions.

Other data have been included in figure 1. The neurone densities in sections of agranular cortex from various primates, determined by Shariff ('53), have been plotted in the same manner. These values were obtained by an indirect method and are higher than those predicted on the basis of the present study. However, the two calculated theoretical slopes are parallel, and the regression coefficient for his data, calculated in the same manner, is -0.28. Similar plots may be made from his data for konio- (striate) cortex from the same primates, with the regression coefficient also being -0.28. In both cases the correlations between the logarithms of neurone density and brain weight were highly significant ($r = -0.98$; for $N = 3$, $P < 0.01$).[5]

There are virtually no figures in the literature concerning neurone density of any mammalian cerebral cortex. In his detailed study of rat cerebral cortex, Sugita ('18a) gives values

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[5] The decrease in neurone density with increasing brain size was noted by Shariff ('53) in his discussion, but no calculations of regression coefficients or of the significance of correlation were made.

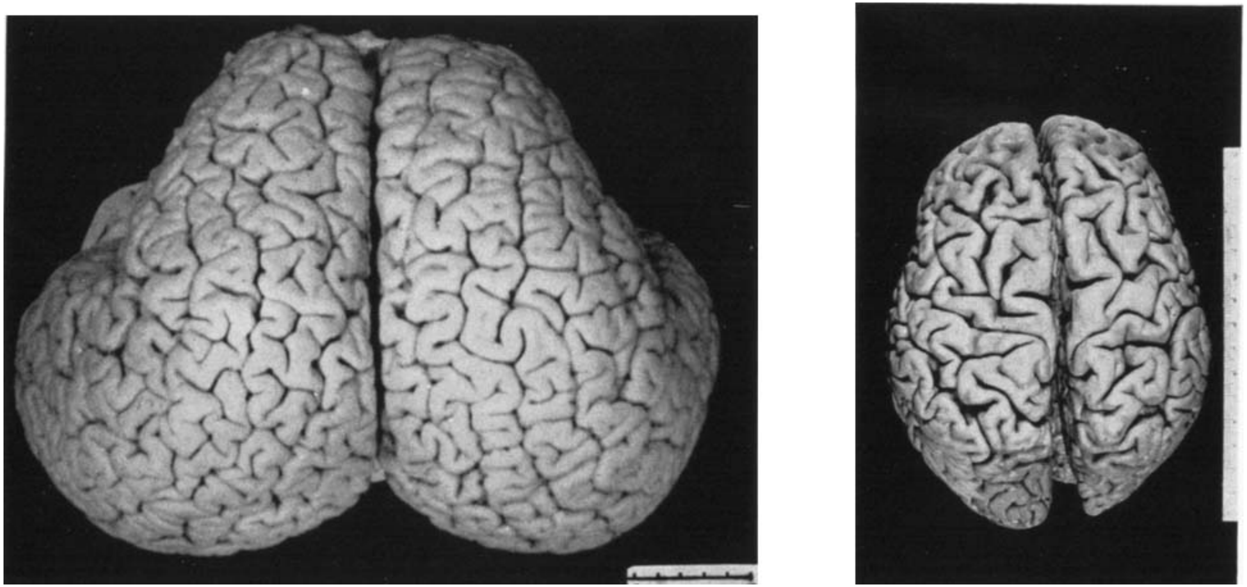

Fig. 2 Photographs of the dorsal aspects of the brain of the adult fin whale, *Balaenoptera physalus* L., (left) and of normal adult man (right). Both brains were formalin-fixed and were photographed without dura or pia-arachnoid at the same magnification (× 1/3). (Scales are in centimeters.)

which average about 80,000 neurones per cubic millimeter. These values were obtained by direct counting, in a manner similar to that used here. His average density, when plotted on figure 1, falls very close to the theoretical position for the rat. Von Economo ('26) gave figures for cortical volume and total number of cells in human cerebral cortex from which an overall average neurone density can be calculated to be about 24,500 neurones per cubic millimeter. This value has been plotted on figure 1 also and falls in the general range expected for human cortex.

Differences in methods, each with certain inherent errors, will not allow absolute comparisons. It is perhaps surprising that the quantitative data are so close. The really significant feature is that with entirely different methods on different species material and in different cortical areas the same relationship between species can be demonstrated to exist.

Microscopic anatomy of fin whale cortex. The histology of the fin whale cortex should be the subject of a separate investigation and is not entirely germane to the present study. Because of the lack of published reports concerning the larger whalebone whales, it seemed desirable to include a brief discussion of the sections used in this study. Of the publications available only a few contain data on the microscopic appearance of cetacean cerebral cortex. The first was published in 1879 by Major for the brain of the Beluga whale *(Delphinapterus leucas)*. In 1893 Kükenthal and Ziehen commented on the cortex of *Hyperoodon rostratus* (the bottle-nosed whale). Subsequently reports by Riese ('25) and Rose ('26) on the "dolphin" cortex and by Langworthy ('32) on the cortex of *Tursiops truncatus* (the bottle-nosed porpoise) have appeared. A study by Bianchi ('05) was not available. Most recently Kojima ('51) has studied and depicted a number of sections of cortex from the sperm whale *(Physeter catodon)*. All except Rose ('26) commented on the similarity in the appearance of Nissl-stained sections taken from various parts of the cortex, on the sparsity of cells, and on the poor differentiation of cell layers. Kükenthal and Ziehen (1893) state: "Der allgemeine

Typus des Aufbaues der Walgehirnrinde ist der Vierschichtige.'' (l.c., p. 103). On the basis of Weigert and Van Gieson stained sections Rose ('26) felt that the usual cell layers and various cortical areas could be distinguished, as in other mammalian cortices. Rawitz ('10) apparently prepared sections from *Balaenoptera rostrata* (the smallest of the *Balaenopteridae*). Apart from a short statement to the effect that the structure of the cortex does not differ from what is known from other mammals, he commented only on the extraordinary length of the apical dendrite of the pyramidal cells. All these studies were carried out on smaller cetacean species with brain weights only slightly greater than man.

Kojima ('51), however, studied the cortex of the sperm whale *(Physeter catodon)*, the brain weight of which is evidently even greater than that of the largest whalebone whales (Jansen, '52). Kojima emphasizes the scarcity of nerve cells in the cerebral cortex and that the differentiation into 6 layers is not fully developed, the differentiation of layers IV, V and VI being particularly poor. In most places layers IV and V were not distinguished so that the cortex seemed to him to have only 5 layers.

As is evident in plates 1 to 4, the fin whale cortex is thinner than human cortex. The neurones appear to be somewhat larger and are certainly much less densely situated. Three cortical layers can be readily distinguished: layer I (''molecular layer'') is very wide; layer II (''outer granular layer'') is narrow and relatively dense in neurones; layer III (''pyramidal layer'') contains very large cells situated very sparsely. Below layer III clear stratification is no longer evident. As noted by previous observers in smaller cetacean brains (Major, 1879; Riese, '25; Langworthy, '32) and by Kojima ('51) in a larger cetacean brain, there seems to be little or no layer IV (''internal granular layer'') in any area of the cortex. What presumably correspond to layers V and VI show no clear stratification and fade off into the white matter, where, as Kükenthal and Ziehen (1893) pointed out, a relatively great number of nerve cells are scattered among the fibres of the white matter. In the innermost portions of the cortex the cell density is very sparse indeed. On the basis of neurone counts in these sections, the neurones in layer II were found to account for at least 50% of all the neurones in a given block of cortex.

This general picture seemed to hold with little variation for all 14 sections studied. It does not seem possible to interpret the peculiarities of cetacean cerebral cortex at present. A more or less distinct row of deeply staining pyramidal cells would seem to demarcate the lower limit of layer III, but Dr. Jansen has suggested that this might also be interpreted as being the beginning of layer V, in which case poorly developed and differentiated layers III and IV would be implied. A fuller discussion will obviously have to await more detailed studies.

The brain of fin whale Cst I was obtained and fixed under good conditions, and the sections were stained within a few weeks of fixation. The appearance of the neurones was not indicative of any evidence of neuronal damage. It has been suggested that frequent submerging of whales for intervals long enough to approach minimal anoxemia over the years might be reflected in signs of neuronal damage. No evidence for supporting this suggestion was seen. Blood vessels were numerous, but an impression of unusually rich vascularization (in keeping with unusual physiological requirements) was not gained from these sections. When stained for Nissl substance, the *space* present in the cortex is impressive. Glial and Golgi stains should be most interesting.

The microscopic appearance of sections of elephant cortex is strikingly similar to that of fin whale cortex. What has been said above regarding the fin whale sections applies equally well to the elephant sections. [It may be recalled that van't Hoog ('20) emphasized the lack of layer IV in the elephant cortex.] In fact it would be difficult to know from the microscopic appearance of the sections alone which species one was studying. In its gross appearance the fin whale brain bears a resemblance to the beef brain, insofar as gyral and sulcal patterns are concerned. This is true also for elephant brain. When the histological appearance of beef cerebral cortex is compared with whale or elephant cortex, allowing for the difference in neurone densities, the same general resemblance holds. Being an ungulate, the elephant might be expected to show this resemblance. But the whale has no close relationship to these two ungulate species. From an evolutionary standpoint, however, it is generally considered that the cetacea derived from a member of the carnivore-insectivore stem from which present-day carnivores and ungulates developed (Kellogg, '28; Howell, '30). Anthony ('26) has offered evidence of certain general anatomical features which are common to some whales and to ungulates. These observations suggest that the resemblances in brain and cerebral cortex may be more than coincidental.

DISCUSSION

The results of this study confirm the observations of Tower and Elliott ('52a) that neurone density in mammalian cerebral cortex decreases with increasing brain weight, according to the equation $N = K_N W^{-0.3}$. From calculations based on the data of Shariff ('53), it is evident that this relationship holds not only for agranular (motor) cortex but also for striate (konio) cortex, and it appears to apply to eulaminate cortex, although present data are not as significant for this type of cortex. The fact that this expression is valid from the smallest mammalian species to species with brains much larger than man is another indication that intelligence does not bear a simple relationship to neurone density and degree of axodendritic complexity in the cerebral cortex. Important as these factors may be, they represent only two of many factors upon which intelligence must depend. On the other hand the correlation of neurone density with brain size is indicative of principles of organization in the cerebral cortex which could be of considerable importance.

The activity of the acetylcholine system bears a similar relationship to brain size (Tower and Elliott, '52a), so that these principles may apply to functional as well as structural organization. The data on acetylcholine activity suggested that activity per unit volume of cortex was proportional to the number of neurones per unit volume of cortex. In order to test this possibility and to define the various relationships more fully, several calculations, based upon data now available, have been attempted. Such calculations must involve certain assumptions and can only, at present, be approximations.

It was shown by Tower and Elliott ('52a) that decrease in activity of the acetylcholine system was correlated with the average total brain weight of each species and was the same function of brain weight for all types of activity measured. Calculations based upon one type of activity would, therefore, be valid for all other types. Because of the greater variety of data available, cholinesterase activity has been chosen for all such calculations.

Preliminary trials made it clear that there is no simple relationship between cholinesterase activity and neurone density. The neurone density of striate cortex is about 4 times that of motor cortex (von Economo, '29; Shariff, '53). Yet the cholinesterase activity (as well as other types of activity) per unit volume of cortex[6] in a given species is the same for these two cortical areas (Nachmansohn, '39; MacIntosh, '41; Feldberg and Vogt, '48; Burgen and Chipman, '51; Tower and Elliott, '52a). Thus, although cholinesterase activity appears to be proportional to the number of neurones in a given cortical area between species, the proportionality is not the same for different cortical areas (see table 2). If the relationship between activity and neurone density is more than coincidental, other factors must be considered.

The size of neurones could be such an additional factor. At present neurone size can only be expressed in terms of volume of the cell body as stained by the Nissl method. In subsequent calculations, figures for neurone volume are understood to be defined in this manner. Detailed data on the human cerebral cortex, published by von Economo ('29), give figures for cortical layers in each area as well as figures for the various cortical areas. With these data results have been obtained which indicate that neurone volume may be a factor in the problem.

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[6] For the purposes of this discussion the specific gravity of the cortex is assumed to be 1.0, which permits the equating of activity per unit weight (the usual method of expression) with activity per unit volume.

For purposes of calculation the distribution of neurones and the average volume of neurones for each layer of cortex were derived from von Economo ('29) for four areas of human cortex: frontal area FD, parietal area PA, occipital area OC, and uncinate area HB (as designated by von Economo). Similar data for rat somato-sensory I cortex were obtained from figures of Pope ('52) for relative numbers of neurones in each layer and average cell dimensions in each layer as determined by the author. Neurone densities for each area of human cortex were derived from the known density of frontal (agranular) cortex (Tower and Elliott, '52a) by use of the ratios between this area and the other respective areas, calculable from the data of von Economo ('29) and Shariff ('53). The density for the area of rat cortex was calculated by the formula of Tower and Elliott ('52a) from the density obtained for the analogous area of human cortex. Mean neurone volumes for each area were derived from the average neurone volumes in each cortical layer and the distribution of neurones per layer for the respective areas.[7] Results of these determinations for human frontal and rat parietal cortex are given in table 1. Results for other areas of human cortex have been summarized in table 2.

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[7] For each cortical area, calculations have been so made that the total column of 5 or 6 layers or cortex represents a total volume of 1 mm^3. Knowing the total thickness of the cortex and the proportion of this identified with each layer, the proportion of the total volume of 1 mm^3 occupied by each cortical layer can be determined. From figures of von Economo ('29) and of Pope ('52) for relative numbers of neurones in each layer and the volume of each layer, the distribution of neurones per layer in relative numbers was determined.

To simplify calculations these results have been expressed as percentages of the total relative density in 1 mm^3. From these percentages the actual numbers of neurones were calculated from the actual densities, based on the value of 10000 per cubic millimeter for frontal agranular cortex (Tower and Elliott, '52a), and were determined by the ratios of the relative totals of neurones in other areas to the relative total for this area (or in the case of rat cortex by the formula $N = K_N W^{-0.3}$ from the density of the analogous human cortical area). The ratios so determined from von Economo's ('29) figures were almost identical with those calculated from the data of Shariff and von Bonin ('53) [The calculations indicated that the density of agranular (motor) cortex and that of area FD of von Economo ('29) were virtually identical, hence the density of this latter area has also been taken as 10000 neurones per cubic millimeter].

Average neurone volumes were calculated from the average dimensions of the cell bodies, given by von Economo ('29) for man and determined for the rat by the author, for each layer by means of the formula of Sugita ('18b, p. 147, footnote 7): $V = \frac{3}{32} \pi (c_1)^2 (c_2)$. To obtain the mean neurone volume for each cortical area, the two values (neurone number and average neurone volume) for each layer were multiplied together, the resultant figures totalled, and the total divided by the neurone density (see table 1).

Where a cortical layer was subdivided, values for the layer as a whole were averaged from the figures for each subdivision, weighted according to the proportion of the layer occupied by each subdivision.

With these data together with cholinesterase activities of human and rat cerebral cortex (Tower and Elliott, '52a) calculations could then be made. In table 2 the cholinesterase activities per neurone and per unit volume of neurone are given for various cortical areas of man and the rat. The activity per neurone is not constant between cortical areas of the same species but varies by a factor of about fifteen. In contrast, the activity per unit volume of neurone is constant both between cortical areas of the same species and between different species. These results suggest that cholinesterase activity is proportional to neurone volume. It is striking that uncinate cortex, which is very different cytoarchitectonically from the other three human cortical areas, should fit so well into this schema. The difference in cholinesterase activity of uncinate cortex, compared to other cortical areas, has also been reported in the dog (Burgen and Chipman, '51), where the difference is of approximately the same order as that found in man.

In table 2 the total volumes occupied by neurone cell bodies per cubic millimeter of cortex have been included. These values were derived from the neurone densities multiplied by the mean neurone volumes for the respective areas. Such values represent a type of "gray/cell coefficient." The values for frontal, parietal and occipital human cortex are of the same order, with uncinate cortex about twice these values. For the rat the value is about 8 times that of the analogous area of human cortex. It is apparent that this is due to the increased neurone density in rat cortex, since the mean cell volume has not changed. These findings are at variance with those of Shariff ('53), who reported a decrease in mean neurone volume with increasing neurone density and found much less difference in "gray/cell coefficient" between small and large brains in his primate series. Olszewski ('53) has observed that comparable neurones in the spinal cord and brain stem of rabbits,

TABLE 1

Distribution and average volume of neurones in layers of human frontal and rat parietal cortex

LAYER [1]	HUMAN FRONTAL CORTEX (AREA FD)				RAT SOMATO-SENSORY I CORTEX			
	Volume of each layer ($\mu^3 \times 10^6$)	Neurones in layer		Average volume of neurones (μ^3)	Volume of each layer ($\mu^3 \times 10^6$)	Neurones in layer		Average volume of neurones (μ^3)
		Per cent of total	Number			Per cent of total	Number	
I	71	1.8	180	65	66	1.5	1950	73
II	71	16.5	1650	120	87	11.0	14300	170
III	286	21.7	2170	1180	182	19.5	25350	500
IV	90	23.5	2350	135	93	19.0	24700	160
V	160	10.5	1050	2300	277	22.0	28600	1300
VI	322	26.0	2600	2060	295	27.0	35100	650
Total	1000		10000		1000		130000	
Mean				1460				600

[1] The column of 6 layers of cortex represents 1 mm^3 total volume in each case.

TABLE 2

Cholinesterase activity per neurone and per unit volume of neurone for various cortical areas of man and the rat

CORTICAL AREA	(1) ChE ACTIVITY (μl CO_2/mm^3/hr.)[2]	(2) NEURONES PER MM^3	(3) MEAN NEURONE VOLUME (μ^3)	(4)[1] TOTAL VOLUME OF NEURONES ($\mu^3 \times 10^6$)	(5)[1] ChE PER NEURONE (μl CO_2/N/hr.)	(6)[1] ChE PER μ^3 OF NEURONE VOLUME (μl CO_2/hr.)
Man:						
Frontal (FD)	1.05	10000	1460	14.6	1.05×10^{-4}	0.75×10^{-7}
Parietal (PA)	1.05	17500	580	10.2	0.6×10^{-4}	1.0×10^{-7}
Occipital (OC)	1.05	38000	230	8.7	0.27×10^{-4}	$1.2 \times 10^{7-}$
Uncinate (HB)	2.6	7000	3780	30.3	3.7×10^{-4}	1.0×10^{-7}
Rat:						
Somato-sensory I	6.5	130000	600	79.0	0.5×10^{-4}	0.85×10^{-7}

[1] Column (4) = column (2) × column (3).

Column (5) = column (1) / column (2).

Column (6) = column (5) / column (3); or column (1) / column (4).

[2] One microliter (μl) of CO_2 is evolved from hydrolysis of 8.1 μg of acetylcholine chloride, using a bicarbonate medium.

monkeys and man show very constant dimensions. It should not be unexpected, therefore, that, while individual neurones in the cortex of larger species may show greater variability in size, the *mean* neurone volume may remain relatively constant for a given area of cortex over a wide range of species. Recently X-ray absorption studies have indicated that in the cerebral cortex the total volume occupied by nerve cell bodies does not exceed 3 to 4% of the total cortical volume, but the percentage of the total solids which the cell bodies account for is much greater than this figure (Pope, '53). In view of these facts, the figures given in table 2 would seem to be reasonable. Rose ('29) has emphasized the differences which can be encountered as a result of varied conditions of fixation of the cortex. The possibility that these factors have modified the data of Shariff ('53) merits consideration. It is interesting that the values for "gray/cell coefficient" for rat and human parietal cortex suggest that this "coefficient" may bear a relationship to brain size similar to that found for neurone density and for acetylcholine activity.

The data already presented are not necessarily indicative of a relationship between activity and neurone volume. The factors of fixation raised in connection with the figures of Shariff ('53) may also be applicable to the limited data given here, and the findings in table 2 could be coincidental. There is, however, another set of observations which support the findings already outlined. Pope ('52) has reported figures for cholinesterase activity in various layers of the primary somatosensory area of rat cortex, and similar figures for human frontal cortex have been published by Pope, Caveness and Livingston ('52).[8] From these data it is possible to derive the percentages of the total cholinesterase activity per unit volume of cortex present in each layer (in a manner analogous to that used to derive the neurone distributions). From these percentages actual activities per layer can be calculated from the known activity per unit volume reported by Tower and Elliott ('52a).

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[8] The human material was obtained from patients undergoing lobotomy procedures. In the present calculations only the figures for the group classed by the authors as "non-psychotic" have been used. Since none of the patients could be considered normal in the strict sense, the figures must be used with reservations.

With these values and the data in table 1, the cholinesterase activity per neurone and per unit volume of neurone has been calculated for each layer of human frontal and rat parietal cortex. The results are found in table 3. With the exception of layer I in each case, the activity per unit volume of neurone is of the same order in every case and approximates the values given in table 2. In view of all the data necessary to arrive at these figures, the degree of agreement obtained would seem to be reasonable. The reason for the discrepancy between values for layer I and those for all other layers are not clear. Layer I is peculiar in several ways. It contains relatively many more processes and fibres in proportion to cell bodies than any other layer. And it contains a relatively much richer vascular network, so that contamination by blood cholinesterases in this layer could be greater than in any other layer. Under the experimental conditions employed by Pope ('52) it was not feasible to control this factor.

In discussing his results Pope ('52) felt that they indicated an identification of cholinesterase activity not with areas of greatest neurone density but with areas of dense axo-dendritic complexes. The results in table 3 would not seem to support that concept.[9] The results suggest that the majority, if not all,

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[9] In his study Pope ('52) also determined the dipeptidase activity per layer of the same area of rat cortex. These results were interpreted by him to indicate an identification of dipeptidase activity with areas of neurone density. Calculations similar to those given here for cholinesterase have been carried out. The results were very similar to those given in table 3, including activity in layer I which was disproportionately high by the same order of magnitude (in Pope's units, $14 \times 10^{-6}/\mu^3$ neurone volume compared to an average of $0.55 \times 10^{-6}/\mu^3$ neurone volume for the other 5 layers). Thus, by the type of calculation used, no apparent difference was observed in the distribution and relationships of these two enzyme activities. Both seemed to be proportional to neurone volume or to some factor dependent thereon. It is of interest that Richter and Hullin ('51) found cholinesterase activity to be present in nuclei as well as cytoplasm of human cortical neurones. If dipeptidase activity is distributed in a similar manner, this observation might account for the similarity in results obtained here.

TABLE 3

Cholinesterase activity per neurone and per unit volume of neurone in layers of human and rat cortex

LAYER [2]	MAN (FRONTAL CORTEX)				RAT (SOMATO-SENSORY CORTEX)			
	ChE in layer		ChE per neurone [1] (μl CO_2/N/hr.)	ChE per μ^3 neurone volume [1] (μl CO_2/hr.)	ChE in layer		ChE per neurone [1] (μl CO_2/N/hr.)	ChE per μ^3 neurone volume [1] (μl CO_2/hr.)
	Per cent of total	Activity (μl CO_2/hr.)			Per cent of total	Activity (μl CO_2/hr.)		
I	11.5	0.12	6.6×10^{-4}	100×10^{-7}	10.0	0.65	3.3×10^{-4}	48×10^{-7}
II	6.0	0.06	0.35×10^{-4}	2.9×10^{-7}	10.0	0.65	0.4×10^{-4}	2.3×10^{-7}
III	35.0	0.36	1.65×10^{-4}	1.4×10^{-7}	22.5	1.45	0.6×10^{-4}	1.2×10^{-7}
IV	5.0	0.05	0.2×10^{-4}	1.5×10^{-7}	8.5	0.55	0.2×10^{-4}	1.2×10^{-7}
V	18.0	0.19	1.8×10^{-4}	0.8×10^{-7}	25.0	1.65	0.6×10^{-4}	0.5×10^{-7}
VI	24.5	0.27	1.05×10^{-4}	0.5×10^{-7}	24.0	1.55	0.5×10^{-4}	0.8×10^{-7}
Total		1.05				6.5		
Average [3]				1.4×10^{-7}				1.4×10^{-7}

[1] ChE per neurone and per cubic micron neurone volume obtained by dividing activities by the respective values in table 1.

[2] For each cortical area, the column of 6 layers represents 1 mm^3 total volume.

[3] Layer I values omitted from averaging.

of the neurones in every layer of the cortex are "cholinergic" in nature. When the decrease in acetylcholine activity per unit of cortex with increasing brain size was first recognized, it was suggested that this might be indicative of a decreasing importance of the acetylcholine system in more highly developed nervous systems (Feldberg, '45; Gerard, '46). Tower and Elliott ('52a) pointed out that their results contradicted this idea insofar as the cerebral cortex was concerned. The results in tables 2 and 3 provide further evidence that there is little indication of a significant difference in "cholinergic" activity between human and rodent cerebral cortex.

Figures in tables 2 and 3 suggest the conclusion that cholinesterase activity is proportional to neurone volume in all three parameters analyzed: (1) between cortical layers in a given cortical area (excepting layer I); (2) between cortical areas in a given species; and (3) between cortices of different species. Neurone volume is the only such measurement which is readily calculable at present. Correlation of activity with neurone volume may be an expression of a relationship to some other important factor, such as surface area, volume and surface area being interdependent. From a functional standpoint the cell surface is very important. Unfortunately necessary data for further consideration of this possibility are lacking. It is of interest that microelectrode recordings from neurones at various depths from the pial surface of the cortex indicate that the amplitude of electrical activity recorded is directly related to the cell size (Jasper and Li, '53). It is not to be inferred that electrical activity is thus referable to activity of the acetylcholine system. The parallelism suggested by these observations raises a possibility which merits further investigation.

An alternative conclusion in regard to the results given in tables 2 and 3 may be entertained. Many neurophysiologists have adopted the schema of Feldberg ('50), which proposes an organization of neurones in the central nervous system into alternating cholinergic and non-cholinergic chains in cortical as well as subcortical structures. It is possible that the results in tables 2 and 3 concern only the segment of cortical neuronal structure which is "cholinergic." If it is assumed that there are "non-cholinergic" segments as well, the results presented would suggest that the "cholinergic" portions constitute relatively constant proportions of the total neurone population in all layers and in all cortical areas in a given species and in cortices between species. It is difficult to visualize the manner in which such a "cholinergic" segment would maintain such a regular organization. The concepts of Bok ('36) may be applicable to this problem. Determination of which, if either, of these alternatives is the more likely will necessitate further investigation.

At present the activity of the acetylcholine system is the only segment of neuronal metabolism which appears to be closely related to number and size of neurones. Respiratory metabolism (oxygen uptake) of mammalian cortex shows no such clear correlation (Elliott, '48; '52). What data there are on glutamic acid metabolism of cerebral cortex fail to indicate any such correlation (Weil-Malherbe, '50; Tower, unpublished). From figures given by Elliott ('48; '52) anaerobic glycolysis per unit of cerebral cortex increases with increases of brain weight, suggesting an inverse relation to neurone density and possibly also to acetylcholine metabolism. Yet these are segments of neuronal metabolism which are recognized to be of fundamental importance to the functioning neurone. These brief considerations suggest that the acetylcholine system occupies a peculiarly intimate position in the metabolism of the neurone. What this is in terms of cortical neuronal function is still far from established.

Some approaches to understanding of the organization of mammalian cerebral cortex have been indicated. It is obvious that data are still far from adequate for such investigations. With more information, valuable applications to problems of disordered neuronal metabolism should be possible. For example, in samples of cortex from human epileptogenic foci, there is an impairment in the ability of such tissue *in vitro* to produce bound acetylcholine (Tower and Elliott, '52b; Tower, '52). Without data on neurone density it would have been difficult to assess the significance of this finding. When it was found that the neurone densities in such abnormally metabolizing epileptogenic cortex did not differ significantly from those in comparable normally metabolizing non-epileptogenic cortex (Tower and Elliott, '52b), the demonstration of this biochemical lesion in epileptogenic cortex assumed great importance. Another example concerns cholinesterase activity in such foci. An increase in cholinesterase activity was found by Pope et al. ('46) in epileptogenic foci induced experimentally in monkeys and by both Pope et al. ('46) and Tower and Elliott ('52b) in human epileptogenic cortical foci. The explanation of this phenomenon is not yet clear, but, on the basis of the foregoing discussion, a number of interesting possibilities and problems arise.

Such problems will become more and more frequent as normal and disordered neuronal activity is investigated at the level of cellular physiology. The data to cope with such problems becomes increasingly essential, if progress in this field of research is to continue.

SUMMARY

1. Neurone densities in the cerebral cortex of the fin whale *(Balaenoptera physalus* L.) were determined in 14 Nissl-stained sections from two adult brains. Densities ranged between 6500 and 7100 neurones per cubic millimeter with an average for all sections of 6800 neurones per cubic millimeter.

2. The total brain weight (without dura) of the adult fin whale, averaged from 9 specimens, was 6785 gm.

3. The average cortical neurone density in three Nissl-stained sections from the brain of an adult Indian elephant was 6900 neurones per cubic millimeter. Total weight of the brain (without dura) was 6075 gm.

4. When average neurone densities for fin whale and elephant cortices, together with cortical neurone densities previously reported for 9 other mammalian species from mouse to man (Tower and Elliott, '52a), were plotted against respective average total brain weights on double logarithmic scales, cor-

tical neurone density was found to decrease regularly with increasing brain weight, according to the equation $N = K_N W^k$ (where N = number of neurones per unit volume; K_N = a constant; W = average total brain weight; and k = regression coefficient for logarithm of N versus logarithm of W for the various species). The value for the regression coefficient, k, calculated to be approximately — 0.3, and correlations between logarithms of neurone density and of brain weight are highly significant ($P < 0.001$) in confirmation of previous findings of Tower and Elliott ('52a).

5. Calculations, based on data of Shariff ('53) for cortical neurone densities in 5 primate species, gave similarly highly significant correlations of neurone density with brain size and values for regression coefficients of — 0.3 in both agranular (motor) and konio (striate) cortex.

6. Because of previous observations that activity of the acetylcholine system bore a similar relationship to brain size (Tower and Elliott, '52a), certain implications of the present findings have been discussed in terms of structural and functional organization of mammalian cerebral cortex.

7. Calculations, based on cholinesterase activity, suggest that activity of the acetylcholine system is proportional to neurone volume (a) between various layers in a given cortical area (excepting layer I); (b) between various cortical areas in a given species; and (c) between cortices of different species.

8. The microscopic appearance of the sections of fin whale and of elephant cerebral cortex have been briefly described.

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PLATES

EXPLANATION OF PLATES 1 TO 4

Photomicrographs of sections of cerebral cortex from the adult fin whale, *Balaenoptera physalus* L., (plate 1) and from normal adult man (plate 2). Both sections were cut at 20 μ, stained for Nissl substance with Gruebler's cresyl violet, and photographed at the same magnification (× 60). The human section was taken from the anterior cingulate gyrus. The fin whale section was taken from a gyrus presumably corresponding to the anterior cingulate gyrus, but from a slightly more posterior location with reference to the anterior commissure.

Photomicrographs of sections of cerebral cortex from the adult fin whale, *Balaenoptera physalus* L., (plate 3) and from normal adult man (plate 4). Both sections were cut at 20 μ, stained for Nissl substance with Gruebler's cresyl violet, and photographed at the same magnification (× 60). The human section was taken from area 2 (of Brodmann). The fin whale section was taken from the medial dorsal aspect of the hemisphere in a region presumably corresponding to parietal cortex posterior to the expected location of the primary somatic sensory area.